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Changes in prevalence of faecal occult blood positivity over time.

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Adenoma, colorectal cancer, faecal immunochemical test, faecal occult blood test, screening

Abbreviations

CI: confidence intervals, CRC: colorectal cancer, FIT: faecal immunochemical test for haemoglobin, FOBT: faecal occult blood test, gFOBT: guaiac faecal occult blood test, ISD: Information Services Division, KPI: key performance indicator, NSS: National Services Scotland, PPV: positive predictive value, SBoSP: Scottish Bowel Screening Programme, UK: United Kingdom.

Abstract

Objectives: Changes in the prevalence of faecal occult blood test positivity over time have not been previously reported, but could have important implications. This study has examined the positivity of the initial guaiac faecal occult blood test (gFOBT), a surrogate marker for colorectal bleeding, in 50-year-old participants in a national bowel screening programme.

Setting: Scottish Bowel Screening Programme.

Methods: Data from the Scottish Bowel Screening Programme (SBoSP) were used to study the initial positivity of the gFOBT between 2007 and 2017. In addition, the positive predictive values (PPV) of the testing process for colorectal cancer (CRC) and adenoma were assessed over the same time period.

Results: Across Scotland, the initial gFOBT positivity increased from 4.1% to 10.8% and, in NHS Grampian and NHS Fife, two of the three NHS Boards which began roll-out of screening in 2007, it increased from 4.0% to 10.9%. In the SBoSP, the PPV for CRC declined from 11.0% to 6.6% and for adenoma it increased from 31.6% to 39.8%.

Conclusions: Over a decade, initial gFOBT positivity increased in 50-year-old participants in the SBoSP. This may be associated with changes in lifestyle and might have implications for screening clinical outcomes, including PPV.

Introduction

In many countries, regular testing for the presence of occult blood in faeces is used for colorectal cancer (CRC) screening,¹ but how the prevalence of detectable blood in faeces changes over time has not been rigorously documented. This is important for several reasons. Firstly, if there is a change in the background prevalence of faecal occult blood test positivity, this could have an impact on the positive predictive value (PPV) of screening using this modality. Secondly, changes in test positivity have implications for service provision in terms of endoscopy capacity. Thirdly, we have recently shown that a positive gFOBT result is associated with premature mortality from all causes, independent of its association with risk of death from CRC,² so that changes in gFOBT positivity may act as an index of possible changes in mortality. To assess changes in gFOBT positivity, this study examined the results of the initial guaiac faecal occult blood test (gFOBT), a surrogate marker for colorectal bleeding, over a decade in 50-year-old participants in a national bowel screening programme.

Methods

In Scotland, CRC screening using a guaiac faecal occult blood (gFOBT) as the first-line investigation was piloted over three screening rounds in three NHS Boards (Tayside, Grampian and Fife) from 2000 to 2007. The Scottish Bowel Screening Programme (SBoSP) was rolled out to the rest of Scotland between June 2007 and December 2009. The algorithm used in the SBoSP differed from those used in the pilot screening rounds, and the details have been described elsewhere³ but,

basically, it consisted of an initial guaiac-based FOBT (gFOBT) where the invitees were asked to provide a total of six faecal samples (two from each of three separate bowel movements) on cards with a window for each sample, followed by a card-based qualitative faecal immunochemical test for haemoglobin (FIT) if one to four windows gave a positive result on the initial gFOBT, a “weak positive” result. If five or six windows were positive on the initial gFOBT or the qualitative FIT was positive, colonoscopy was offered immediately. This two-tier reflex gFOBT/FIT algorithm continued until November 2017 when it was replaced by a single faecal sample quantitative FIT.⁴ All samples were analysed in the Scottish Bowel Screening Laboratory which holds ISO 15189 accreditation. The Laboratory performed comprehensive internal quality control, including assessment of individual screener staff performance, both analytically and through monitoring of positivity reported. Since gFOBT requires visual interpretation of the colours on the test card, all positive test results were confirmed by a second screener. External quality assessment was undertaken through participation in the United Kingdom National External Quality Assessment Scheme (UKNEQAS). Acceptance quality checks were undertaken for all new manufacturing lots of gFOBT and FIT.⁵ There were no significant changes in the testing processes, faecal test characteristics, or gFOBT manufacturer and supplier, from 2000 to 2017. The instructions given to participants did not change during the study: no dietary restrictions, including vitamin C intake, nor cessation of medicines such as non-steroidal anti-inflammatory drugs and anti-coagulants, were advocated.

Estimation of changes in gFOBT positivity over time using data from the SBoSP is not straightforward. Firstly, if all results were used, the data would comprise a mixture of prevalence (first time) and incidence (repeat) screening and from

participants of a range of ages between 50 and 74 years, the proportions of which changes over time. Since it is known that the gFOBT positivity in incidence screening is less than that of prevalence screening⁶ and increases with age,⁷ it would be difficult to disentangle these effects from a true change in gFOBT positivity in the whole population accepting screening. Secondly, since the SBoSP was being rolled out between 2007 and 2009, and the effect of adding a screening naive NHS Board takes two years (a single screening round) to be complete, the screened population has only been geographically stable since the end of 2011. Since the gFOBT positivity varies considerably between NHS Boards,⁸ possibly as a result of varying degrees of socio-economic deprivation, this adds another effectively uncontrollable variable. Thirdly, since the final result in the context of the SBoSP, up until November 2017, is derived from an algorithm that, by design, cuts-down the overall positivity and minimises false positive results by excluding a high proportion of those participants who exhibit lower (weak) degrees of positivity on the initial gFOBT (only a small proportion of those with one to four windows positive on this initial gFOBT have a positive FIT result³), using the overall final result of the screening algorithm to assess variation in gFOBT positivity over time would underestimate any changes.

For these reasons, this study examined the overall positivity of only the initial gFOBT, not the final positivity of the overall screening algorithm, that is, the positivity in those who had any one or more windows positive, but *only* in 50-year-old participants. This ensured that all subjects in this study were the same age and were undergoing only prevalence screening. This initial gFOBT positivity was determined for every year from 2007 to 2017 for the whole of Scotland and, to eliminate the possible effect of adding different NHS Boards during roll-out of the SBoSP, an additional analysis was

carried out restricted to NHS Grampian and NHS Fife; along with NHS Tayside, these two NHS Boards were the first to participate in the roll-out of the SBoSP in 2007, having taken part in the three pilot screening rounds from 2000 to 2007.⁶ However, NHS Tayside performed an evaluation of quantitative FIT as the first-line screening test between 01 July 2010 and 31 December 2010,⁹ and was therefore excluded from the analysis since, during this time, this could have introduced a spurious fluctuation in positivity.

The data for these analyses were obtained from the Bowel Screening Database held by the Information Services Division (ISD) of National Services Scotland (NSS). Data from the pilot screening rounds could not be studied, since the overall positivity rate of the initial gFOBT was not recorded, only the final outcome of the screening algorithms used in these three rounds. Formal ethical approval for the study was not required since individual participants were not approached and only routinely collected data were used. Researchers wishing to access these data can apply for permission via the ISD's Electronic Data, Research and Innovation Service (NSS.eDRIS@nhs.net).

Results

For the whole of Scotland, there was a steady rise in gFOBT positivity (i.e., any positive window on the initial gFOBT card) in 50-year-old participants from 4.1% (95% confidence intervals [CI]: 3.7 - 4.6) in 2007 to 10.8% (95% CI: 10.3 - 11.3) in 2017 (Figure 1). In NHS Grampian and NHS Fife (Figure 2) a similar rise was seen: 4.0% (95% CI: 3.5 - 4.6) to 10.9% (95% CI: 9.7 - 12.1). As evidenced by the wide separation of the higher confidence intervals for the 2007 data and the lower confidence intervals for the 2017 data, these differences were highly statistically

significant ($p < 0.00001$ by χ^2 testing in both instances). Positivity rates for women were lower than that for men, as has been found previously overall in the SBoSP,⁷ although these did converge in 2017 in NHS Grampian and NHS Fife.

For completeness, the final results of the screening algorithm (derived from the gFOBT/FIT two-tier reflex approach) were also examined, and the positivity in those aged 50 years for the whole of Scotland increased from 0.68% (95% CI: 0.53 - 0.88) to 1.6% (95% CI: 1.4 - 1.7) ($p < 0.00001$ by χ^2 testing) between 2007 and 2017. This supports the view that the rise in initial gFOBT positivity was indeed due to the presence of occult blood in faeces and not to other moieties, since these would not be detected by the qualitative FIT used to determine the need for further investigation in those participants with one to four windows (weak) positive, since the qualitative FIT used is based upon the reaction with antibodies specific to the globin moiety of human haemoglobin.

Since a change in background gFOBT positivity could affect the positive predictive value (PPV) for neoplasia, the PPV for both CRC and adenoma over time were also examined. By necessity, this had to be calculated on the basis of those who had a final positive test result based on the whole screening algorithm, but as described in the preceding paragraph the positivity derived in this way has also increased during the study period. Between 2007 and 2017 the PPV for CRC fell from 11.0% to 6.6% ($p < 0.00001$ by χ^2 testing) as shown in Figure 3 and for adenoma it increased from 31.6% to 39.8% ($p < 0.00001$ by χ^2 testing) as shown in Figure 4.

Discussion

To our knowledge, this is the first time that the change over time of faecal occult bleeding, as inferred from initial gFOBT positivity, has been reliably investigated. It is true that gFOBT provide an indirect measure of gastrointestinal, particularly colorectal, bleeding since it is based on a chemical reaction that can give false positive results from peroxidase containing materials in the diet and dietary restriction was not mandated in the SBoSP. However, there is evidence that, when gFOBT cards are allowed to dry for some days prior to development in the laboratory, as was the case in the SBoSP, such dietary effects are negligible.^{10,11}

Using FIT would clearly provide a more secure estimate of the presence of occult blood in faeces, but there are no screening programmes using this approach that are of sufficient duration to study the change in faecal haemoglobin concentration over time. However, this will be interesting to study in the future, both in the nations of the UK and other countries, especially as FIT is now replacing gFOBT world-wide.

The reason behind this highly likely increase in faecal occult bleeding in the population studied is not clear, but it is noteworthy that our recent study of gFOBT results and all-cause mortality showed that a positive gFOBT result was associated with an increase in all-cause mortality, in all non-CRC mortality and in death from a variety of chronic conditions including cardiovascular disease, respiratory disease and cancer excluding CRC.² In this study, it was demonstrated that this effect was independent of medicines that could cause bleeding, such as anti-coagulants and aspirin and other non-steroidal anti-inflammatory medicines, and the hypothesis was generated that a positive gFOBT result, implying gastrointestinal bleeding, might reflect systemic inflammation caused in turn by factors predisposing to ill health,

such as obesity,^{12,13} sedentary behavior,^{14,15} smoking,¹⁶ alcohol dependence¹⁷ and a “Western” diet.^{18,19}

Thus, the rise in initial gFOBT positivity seen in the ten-year interval between 2007 and 2017 could be related to changing lifestyle factors. Trends data from the Scottish Health Survey from 2008 to 2017 report less than ideal levels of physical activity, fruit and vegetable intake, alcohol, smoking and obesity in adult men and women aged 45 to 54 years.²⁰ However, it is notable that the only lifestyle risk factor which has increased during this time in this age group is obesity (from 30% to 36% prevalence in men and 29% to 34% prevalence in women) which, given that physical activity has increased, implies that caloric intakes have increased. Obesity *per se* is associated with increased inflammation and changes in the microbiota,²¹ which might in turn influence gFOBT results. It is also of interest of note that, in Scotland, average life expectancy is beginning to decline,²² which is in keeping with our observations.

The hypothesis that faecal haemoglobin concentrations are a reflection of systemic inflammation could be addressed by carrying out a similar study using faecal calprotectin, or possibly other markers of inflammation, but this is impractical given the time scales involved. It is relevant to note, however, that in our study of gFOBT positivity and all-cause mortality, a number of non-neoplastic causes of death known to be associated with systemic inflammation were also associated with a positive gFOBT result.²

Quite apart from any public health implications of this observation, an increase in the background rate of faecal occult bleeding that is unrelated to the incidence of CRC could impact on the overall performance of a population-based programmatic CRC

screening programme predicated on the detection of the presence of occult blood in faeces through decreasing the positive predictive value (PPV) of the test result. In the SBoSP, the PPV of a final test result for both CRC and adenoma have been key performance indicators (KPI) since the beginning of the SBoSP.⁷ Examination of the PPV for CRC over time demonstrated that there was indeed a decline in the PPV between 2007 and 2017 from 11.0% to 6.6% leading to a small decrease in cancer detection rate in those with a final screening test result,⁷ albeit accompanied by an increase in overall uptake, as has been described in detail.²³ This could be explained by a decrease in the ratio of prevalence to incidence screening episodes or changes in colonoscopy quality, although in Scotland, as we have described,²⁴ no new measures were introduced to improve or audit colonoscopy performance throughout the study periods. However, an increase in background population gFOBT positivity is an alternative or additional explanation and this could be interpreted as an inherent weakness of this approach to screening.

However, the PPV for adenoma increased between 2007 and 2017 from 31.6% to 39.8%. This is in keeping with the hypothesis that adenomas are detected by tests for the presence of occult blood in faeces, not simply because they bleed, but because chronic inflammation is involved in the initiation of the neoplastic process so that adenomas tend to arise in a sub-clinically inflamed colon. If this is the case, an increase in faecal occult bleeding in the population might signal an increase in the incidence of colorectal adenomas. Thus, testing for the presence of occult blood in faeces might prove to be an effective means of finding adenomas that will take account of changes in incidence, especially if the faecal haemoglobin concentration threshold for triggering a colonoscopy from quantitative FIT is lowered. This in turn

could enhance the ability of screening programmes to prevent the development of invasive CRC by interrupting the adenoma-carcinoma sequence.

Conclusions

Over a decade, initial gFOBT positivity increased in 50-year-old participants in the SBoSP. This may be associated with changes in lifestyle and might have implications for screening clinical outcomes, including PPV.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: NHS Tayside, through CGF, had a paid consultancy contract with Immunostics Inc., Ocean, NJ, USA, the suppliers of gFOBT and qualitative FIT. All other authors declare no conflicts of interest.

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References

1. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. *Int J Cancer* 2012; 130: 2961-2973.
2. Libby G, Fraser CG, Carey FA, Brewster DH, Steele RJC. Occult blood in faeces is associated with all-cause and non-colorectal cancer mortality. *Gut* 2018; 67: 2116-2123.
3. Fraser CG, Digby J, McDonald PJ, et al. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. *J Med Screen* 2012; 19: 8-13
4. <https://nhsnss.org/blog-news/articles/new-bowel-cancer-screening-test-launched/>
5. McDonald PJ, Anderson CM, Fraser CG. Acceptance quality checks for qualitative fecal immunochemical tests ensure screening program consistency. *Int J Cancer* 2011; 128: 247-248.
6. Steele RJC, McClements PL, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* 2009; 58: 530-535

7. Steele RJC, Kostourou I, McClements P, et al. Effect of gender, age and deprivation on key performance indicators in a FOBT based colorectal screening programme. *J Med Screening* 2010; 17: 68-74
8. <http://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/>
9. Steele RJC, McDonald PJ, Digby J, et al. Clinical outcomes using a faecal immunochemical test for haemoglobin in a national colorectal cancer screening programme constrained by colonoscopy capacity. *U Eur Gastroenterol J* 2013; 1: 198-205.
10. Sinatra MA, St John DJ, Young GP. Interference of plant peroxidases with guaiac-based fecal occult blood tests is avoidable. *Clin Chem* 1999; 45: 123-126.
11. Pignone M, Campbell MK, Carr C, Phillips C. Meta-analysis of dietary restriction during faecal occult blood testing. *Eff Clin Pract* 2001; 4: 150-156.
12. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. *J Endocrinol* 2014; 222: R113-127
13. Cox AJ, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol* 2015; 3: 207-215.

14. Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab* 2013; 15: 51-60.
15. Silverman MN, Deuster PA. Biological mechanisms underlying the role of physical fitness in health and resilience. *Interface Focus* 2014; 4: 20140040.
16. Rom O, Avezov K, Aizenbud D, Reznick AZ. Cigarette smoking and inflammation revisited. *Respir Physiol Neurobiol* 2013; 187; 5-10.
17. Ippolito JA, Curtis BJ, Choudhry MA, Kovacs EJ. Alcohol and immunology: Summary of the 2012 Alcohol and Immunology Research Interest Group (AIRIG) meeting. *Alcohol* 2013; 47: 589-593.
18. Huang EY, Devkota S, Moscoso D, Chang EB, Leone VA. The role of diet in triggering human inflammatory disorders in the modern age. *Microbes Infect* 2013; 15: 765-774.
19. Thorburn AN, Macia L, Mackay CR. Diet, metabolites and “Western-lifestyle” inflammatory diseases. *Immunity* 2014; 40 :833-842.
20. <https://www2.gov.scot/Topics/Statistics/Browse/Health/scottish-health-survey/Publications/Trend2017>
21. Cox AJ, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol* 2015; 3: 207-215.

22. <https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/life-expectancy/life-expectancy-at-scotland-level/scottish-national-life-tables/2015-2017> Accessed 22/05/2019
23. Quyn AJ, Fraser CG, Stanners G, et al. Uptake trends in the Scottish Bowel Screening Programme and the influences of age, sex, and deprivation. *J Med Screen* 2018; 25: 24-31.
24. Quyn AJ, Fraser CG, Stanners G, et al. Scottish Bowel Screening Programme colonoscopy quality - scope for improvement? *Colorectal Dis* 2018; 20: O277-O283.

Figure 1. Change in the positivity of the initial gFOBT in 50-year-old participants in the Scottish Bowel Screening Programme between 2007 and 2017 for the whole of Scotland. ($X^2= 305.6$ $p<0.00001$).

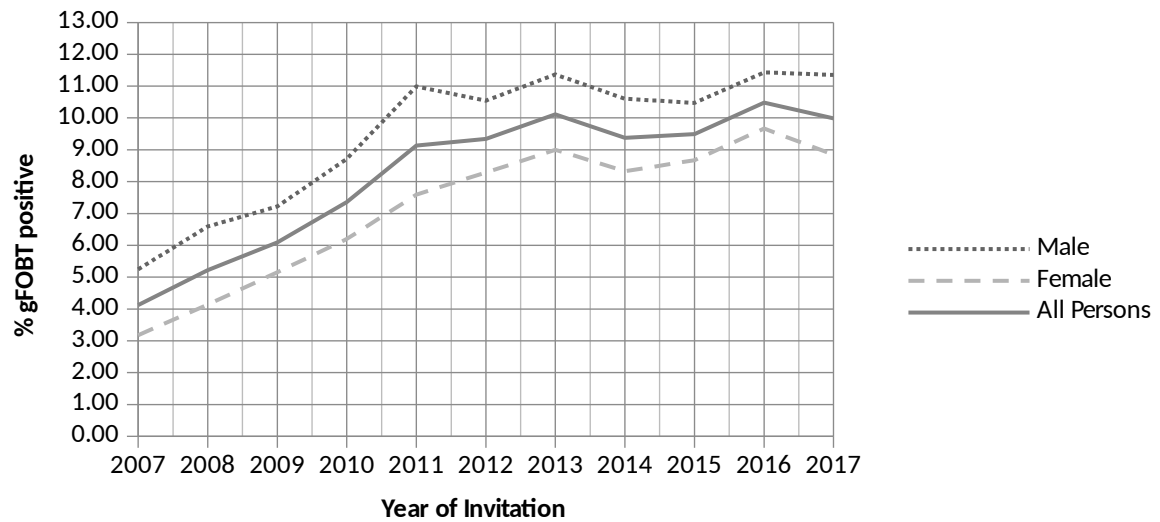


Figure 2. Change in the positivity of the initial gFOBT in 50-year-old participants in the Scottish Bowel Screening Programme between 2007 and 2017 from NHS Grampian and NHS Fife Boards only. ($X^2= 115.1$ $p<0.00001$).

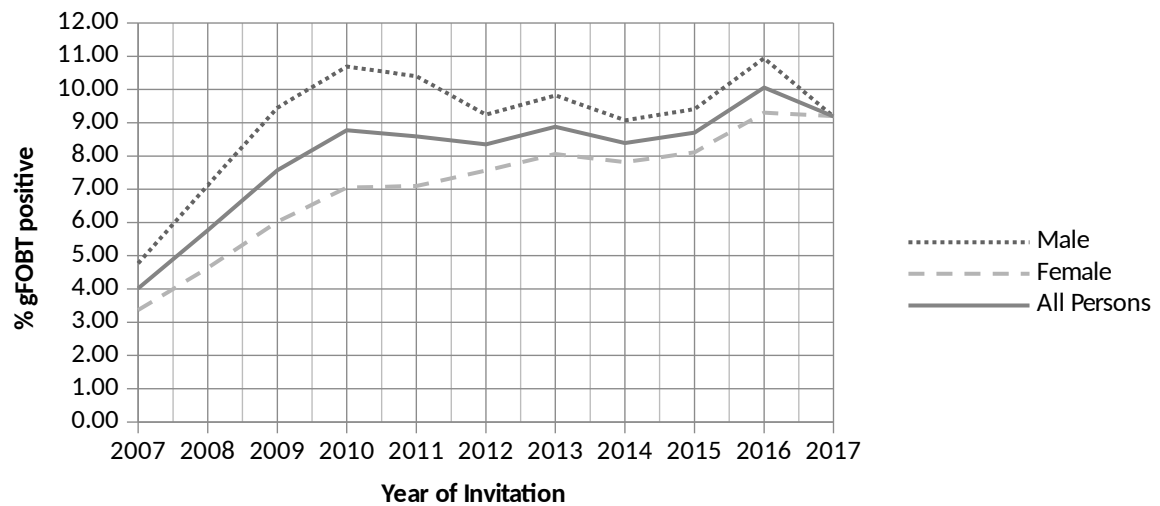


Figure 3. Positive predictive value for colorectal cancer in the Scottish Bowel Screening Programme between 2007 and 2017 ($\chi^2=24.8$ $p<0.00001$).

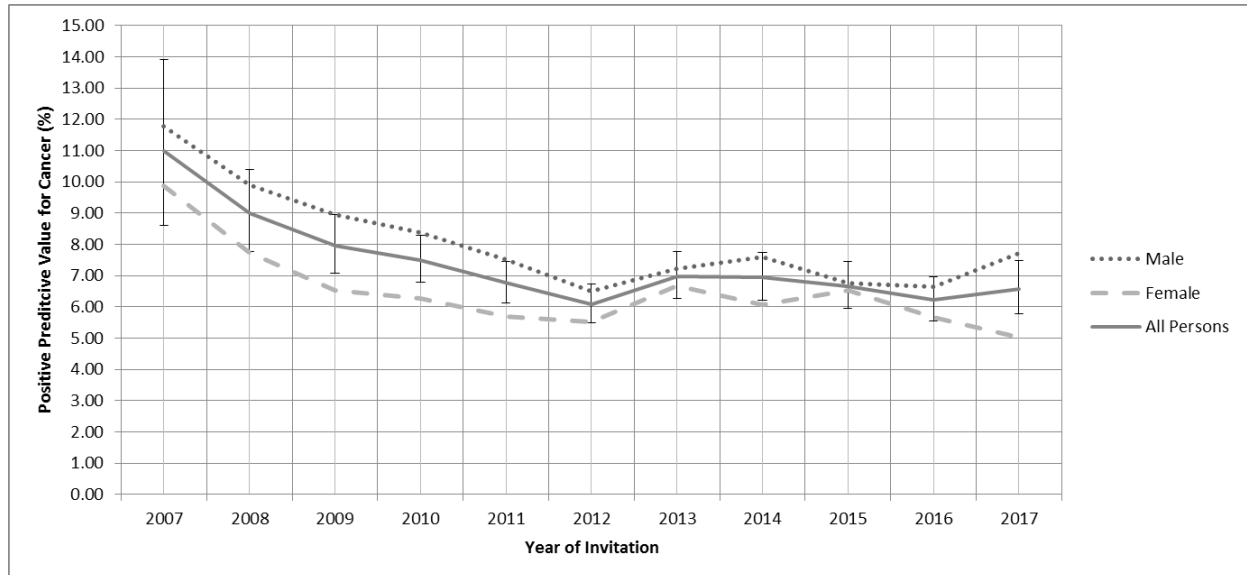


Figure 4. Positive predictive value for adenoma in the Scottish Bowel Screening Programme between 2007 and 2017 ($\chi^2=23.4$ $p<0.0001$).

